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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

TXR No.: 0054172

MEMORANDUM

DATE: March 23, 2006

SUBJECT: **ETHABOXAM:** Report of the Cancer Assessment Review Committee
PC Code: 090205

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

Jessica Kidwell

TO: Karlyn Bailey, Toxicologist (RAB2)
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Health Effects Division (7509C)

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Fungicide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on February 15, 2006 to evaluate the carcinogenic potential of ETHABOXAM. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

APR 13 P.M.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF ***ETHABOXAM***

PC CODE 090205

March 23, 2006

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION

Karlyn Bailey, Toxicologist

DOCUMENT PREPARATION:

Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise stated).

Lori Brunsman, Statistician

William Burnam, Chair

Marion Copley

Vicki Dellarco

Kit Farwell

Abdallah Khasawinah

Nancy McCarroll

Tim McMahon

Esther Rinde

Jess Rowland

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Alan Levy (HED/RAB2), Robert Mitkus (HED/RAB1), Kelly Schumacher(HED/RAB2), Whang Phang (HED/RRB1)

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EXECUTIVE SUMMARY

On February 15, 2006, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Ethaboxam. This was the first time that this compound was assessed for carcinogenicity by the CARC.

Karlyn Bailey of Registration Action Branch 2 presented the chronic toxicity/carcinogenicity study in Sprague Dawley rats and the carcinogenicity study in CD-1 mice. Ethaboxam (99%) was administered in the diet to Crl:CD(SD)BR rats (60/sex/dose) at dose levels of 0, 100, 300, or 650 ppm (approximately equivalent to 0, 5.5, 16.4, or 35.8 mg/kg/day in males and 0, 7, 21, or 45.5 mg/kg/day in females) for 104 weeks. Ethaboxam (99.0% a.i.) was administered in the diet to Crl:CD-1(ICR)BR mice (50/sex/dose) at dose levels of 0, 100, 300, or 900 ppm (approximately equivalent to 0, 12, 35, or 117 mg/kg/day in males and 0, 14, 44, or 135 mg/kg/day in females) for up to 78 weeks. She also presented information on mutagenicity, structure activity relationship, and mode of action data for Leydig cell tumors.

The CARC concluded the following:

Carcinogenicity

Rat

• In male Sprague Dawley rats, the incidence of benign testicular Leydig cell tumors was 1/56 (2%), 4/56 (7%), 6/59 (10%), and 7/58 (12%) for the control, 100, 300 and 650 ppm dose groups, respectively. The CARC considered the increase in benign Leydig cell tumors of the testes to be treatment-related based on the following:

-There was a significant increasing trend, and a significant difference in pair-wise comparison of the 650 ppm dose group with the control for benign interstitial (Leydig) cell tumors of the testes, both at $p < 0.05$.

-The incidences of interstitial cell tumors in all treated groups (7-12%) exceeded the historical control incidence rates for the testing laboratory (2.5% average, 0-6.2%, range). Therefore, the increased incidences of interstitial cell tumors at 300 ppm and possibly 100 ppm, while not statistically significant, were considered to be biologically significant.

•There were no treatment-related tumors seen in female Sprague Dawley rats.

•Adequacy of Dosing: The CARC considered the highest dose tested (650 ppm) in male and female rats to be adequate, but not excessive, to assess the carcinogenicity of ethaboxam. This was based on decreased body weight gain in males (20%) and females (17%) and toxicity of male reproductive organs, including non-neoplastic lesions of the testes, epididymides, prostate, and seminal vesicles.

Mouse

• In male CD-1mice, the incidence of liver tumors (adenomas and/or carcinomas combined) was 13/45 (29%), 13/48 (27%), 18/47 (38%), 20/46 (43%) for the controls, 100, 300, and 900 ppm dose groups, respectively. The CARC did not consider these tumors to be treatment-related based on the following:

- Male mice had a statistically significant trend for liver adenomas and/or carcinomas combined only at $p<0.05$ ($p=0.043$). There were no statistically significant pair-wise comparisons of the dosed groups with the controls for adenomas, carcinomas, or combined adenomas and/or carcinomas.
- It is noted that the incidence of adenomas in the concurrent control (29%) was high and outside the historical control range of the testing laboratory (14-24%) as well as the historical control range from Charles River Laboratories (2.9-28%). While the incidence of liver adenomas was outside the historical control range for all treated groups, there was no significant trend or significant pairwise comparisons of the dosed groups with the controls for liver adenomas at any dose level.

• There were no treatment-related tumors seen in female CD-1 mice.

• Adequacy of Dosing: The CARC considered the highest dose tested (900 ppm) in male and female mice to be adequate, but not excessive, to assess the carcinogenicity of ethaboxam. This was based on decreased body weight body weight (9%) and body weight gain (20%) in males and females at 900 ppm, decreased food efficiency, increased liver weights in females, and liver pathology in females and lung pathology in males.

Mutagenicity

Based on the findings, it was concluded that ethaboxam is not mutagenic in bacteria or mammalian cells. There is, however, equivocal evidence of a clastogenic effect in the *in vitro* human lymphocyte chromosome aberration assay. In contrast, the test material was neither clastogenic nor aneugenic in the mouse bone marrow micronucleus assay up to the limit dose. Although the weight-of-evidence does not support a mutagenic concern, the Committee recommends that the *in vitro* cytogenetics assay be repeated to clarify the earlier results.

Structure-Activity Relationship

There are no suitable structural analogues for ethaboxam at this time, however, the 2-amino thiazole moiety can be considered a structural alert for ethaboxam.

Mode of Action

> The overall weight of evidence suggests that ethaboxam is a testicular toxicant in the rat, capable of producing marked damage. However, based on the available data, it is unclear whether the mechanism leading to Leydig cell tumors is a result of a hormonally-mediated pathway. The existing mode of action data are inadequate as a basis for delineation of a plausible sequence of key events leading to Leydig cell tumors (i.e., decreased testosterone and chronic stimulation of interstitial cells by elevated luteinizing hormone (LH) levels). While there was a suggestion of decreased testosterone and a slight increase in LH, the hormonal data did not support a consistent pattern, either temporally or through dose-response concordance. Therefore, the decrease in testosterone and increase in LH cannot be clearly linked with increases in Leydig cell tumors.

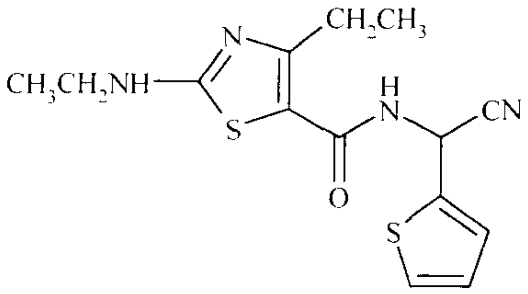
In accordance with the EPA's Final Guideline for Carcinogen Risk Assessment (March 2005), the CARC classified Ethaboxam as **"Suggestive Evidence of Carcinogenic Potential"**. This was based on the following weight-of-evidence considerations: (i) There was a treatment-related increase in only one tumor type (benign Leydig cell tumors of the testes) in one species (Sprague Dawley rat); (ii) No treatment-related tumors were seen in female rats or male or female mice; (iii) Ethaboxam does not appear to be a gene mutagen, however, the clastogenic potential of this compound can not be determined at this time; (iv) The registrant's proposed hormonally-mediated pathway is biologically plausible, but the available data are insufficient to delineate the sequence of key events leading to Leydig cell tumors that are necessary to characterize human relevance of this animal response.

I. INTRODUCTION

On February 15, 2006, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Ethaboxam.

II. BACKGROUND

Chemical Name:	Ethaboxam
IUPAC Name:	(RS)-*N*-(-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5-carboxamide
Other Name:	*N*-(cyano-2-thienylmethyl)-4-ethyl-2-(ethylamino)-5-thiazolecarboxamide
CAS Registry No.:	162650-77-3
PC Code:	090205
Structure:	



Ethaboxam (LGC-30473) is a thiazole carboxamide fungicide with preventative and systemic activity for the control of downy mildew on grapevines. It has been registered in South Korea since 1999 and is currently on the registration track in many European countries. LG Life Sciences, Ltd has submitted a tolerance petition (PP#4E6863) to allow the legal importation of grapes (and its processed commodities) grown outside of the United States. There are currently no registered domestic uses of ethaboxam in the U.S., and no ethaboxam tolerances are established.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Sprague-Dawley Rats

Combined Carcinogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks (2002). Laboratory Project No. LKF002/984932. August 28, 2002. MRID 46387811.

A. Experimental Design

Ethaboxam (99%) was administered in the diet to Crl:CD(SD)BR rats (60/sex/dose) at dose levels of 0, 100, 300, or 650 ppm (approximately equivalent to 0, 5.5, 16.4, or 35.8 mg/kg/day in males and 0, 7, 21, or 45.5 mg/kg/day in females) for 104 weeks. Groups of 20 males and 20 females were administered the same diets and sacrificed at 52 weeks.

B. Discussion of Survival and Tumor Data

Survival Analysis

TOXICITY PHASE
There were 4 deaths (1 control, 1 mid-dose, and 2 high-dose) during the first 52 weeks of treatment. There was nothing about the incidence of these deaths or the findings at necropsy to suggest a treatment-related effect on survival during the first year of the study.

CARCINOGENICITY PHASE
There were no statistically significant incremental changes in mortality with increasing doses of ethaboxam in male or female rats (Memo, L. Brunsman, 1/25/06, TXR# 0054055). The overall survival rates in treated male rats were comparable to those of the control group. Survival was much lower in all groups of female rats than in male rats. Histopathological examination revealed increased incidences of pituitary tumors of the pars distalis in females as possibly contributing to the lower survival rate. Survival in both sexes met the guideline requirements of 50% at week 78 and 25% at week 104.

Tumor Analyses

Males
Male rats had a statistically significant trend, and a statistically significant pair-wise comparison of the 650 ppm dose group with the controls, for testicular interstitial cell tumors, both at $p < 0.05$. The statistical analyses of the male rats were based upon the Exact test for trend and Fisher's Exact test for pair-wise comparisons (Table 1, Memo, L. Brunsman, 1/25/06, TXR# 0054055).

The incidences (7-12%) of interstitial cell adenoma in treated groups in the testes exceeded that of historical controls, which ranged from 0-6.2% with an average of 2.5%. The historical control

data for interstitial cell tumors of the testes in male rats, provided by the Registrant, included data from 8 studies (50-65 animals/study); the study dates were not provided. Historical control data from Charles River Laboratories (Giknis and Clifford, 2001), included data for 1531 testes from male CRl:CD(SD)BR control rats tested approximately 104 weeks in 23 studies initiated between 1991-1997. Of these testes, 36 (2.4%), in 14 separate studies, had adenomas. In the 14 studies where tumors were observed, the percent affected ranged from 1.43-7.14%.

Table 1. Ethaboxam - Crl:CD Rat Study (MRID 46387811)

Male Testes Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)			
Tumor Type	**0**	**100**	**300**	**650**
Interstitial Cell Tumors (%)	1/56 (2)	4/56 (7)	6[a]/59 (10)	7/58 (12)
p =	0.03125*	0.18179	0.06538	0.03408*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First interstitial cell tumor observed at week 78, dose 300 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical controls: interstitial cell adenoma, range = 0-6.2%; average = 2.5%

Females

There were no statistically significant findings, either trend or pair-wise, for pituitary tumors in female rats (Table 2, L. Brunsman). The incidences of adenoma were 35/77 (45%), 44/79 (56%), 47/80 (59%), and 39/80 (49%), the incidences of adenocarcinoma were 10/77 (13%), 9/79 (11%), 9/80 (11%), and 15/80 (19%), and the incidences of adenoma/adenocarcinoma combined were 45/77 (58%), 53/79 (67%), 56/80 (70%), and 54/80 (68%) in females at 0, 100, 300, and 650 ppm, respectively. The incidences of pituitary adenoma in females at 300 ppm, adenocarcinoma at 650 ppm, and adenoma/adenocarcinoma combined at 300 and 650 ppm, were slightly above the upper range of historical controls (adenoma, 56-70%; adenocarcinoma, 2-15%; combined, 68-82%); however, the lack of any statistically significant findings, including a clear dose-related trend, and the extremely high incidence in the controls suggest that the increased incidences are not treatment-related.

The historical control data for pituitary tumors in female rats, provided by the Registrant, included data from 7 studies (50-65 animals/study); the study dates were not provided.

Historical controls: pituitary adenoma, range = 56-70%
pituitary adenocarcinoma, range =2-15%
pituitary adenoma/adenocarcinoma combined, range = 68-82%

Historical control data from Charles River Laboratories (Giknis and Clifford, 2001), included data for 1729 pituitary glands from female CRl:CD(SD)BR control rats tested approximately 104 weeks in 24 studies initiated between 1991-1997. Of these pituitary glands, 1206 (69.8%), in 24 separate studies, had adenomas. In the 24 studies where tumors were observed, the percent affected ranged from 26-92%. Carcinomas were present in 117 pituitary glands (6.8%) in 18 studies. In the 18 studies with tumors, the percent affected ranged from 1.4-58%.

Table 2. Ethaboxam - Crl:CD Rat Study (MRID 46387811)
Female Pituitary Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)			
Tumor Type	0	100	300	650
Pituitary Adenomas (%)	35/77 (45)	44/79 (56)	47[a]/80 (59)	39/80 (49)
p =	0.4972	0.1315	0.0657	0.4000
Pituitary Adenocarcinomas (%)	10/77 (13)	9[b]/79 (11)	9/80 (11)	15/80 (19)
p =	0.1058	0.7083	0.7183	0.2215
Pituitary Adenomas Adenocarcinomas Combined (%)	45/77 (58)	53/79 (67)	56/80 (70)	54/80 (68)
p =	0.1768	0.1707	0.0893	0.1562

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 45.

[a]First adenoma observed at week 45, dose 300 ppm.
[b]First adenocarcinoma observed at week 50, dose 100 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Non-Neoplastic Lesions in Crl:CD BR (SD) Rats

The non-neoplastic lesions in male and female rats treated with ethaboxam are presented in Table 3. In a combined chronic toxicity/carcinogenicity study, after 52 weeks (toxicity phase), 35% ($p<0.01$) of 650 ppm male rats had abnormal spermatogenic cells in the duct of the epididymis compared with none of the controls. Abnormal spermatogenic cells also were observed in three and four male rats in the 100 and 300 ppm groups, respectively. There was no clear dose-related increase in severity of the epididymal lesion in male rats. The incidences of other lesions in the epididymis of treated male rats were not significantly increased in the toxicity phase of the study. Bilateral seminiferous tubular atrophy was observed in 15, 20, and 28% (not statistically significant; N.S.) of males in the 100, 300, and 650 ppm groups, respectively, compared with only 5% of controls. The incidence of unilateral + bilateral seminiferous tubular atrophy was marginally increased in males in the 300 and 650 ppm groups. The increased incidence of lesions in the testes and epididymides indicates that the male reproductive organs are targets of the test material. Generalized hepatocyte hypertrophy was observed in two 650 ppm males and centrilobular hepatocyte hypertrophy was observed in one 650 ppm male compared with none of the controls (not listed in Table 3). Female rats at 650 ppm in the toxicity phase had significantly increased incidences of focal acinar cell atrophy in the pancreas (35%, $p<0.01$) and hyperplasia in the pars distalis of the pituitary (30%, $p<0.05$) compared with 0% in the control group for both lesions. The incidence of ovaries with absent corpora lutea also was significantly increased in females of the 650 ppm group (40%, $p<0.05$) compared with that of controls (10%). No other notable histopathological lesions were observed in the toxicity portion of the study.

In the carcinogenicity phase, male rats had increased incidences of lesions in the testes, epididymides, prostate, and seminal vesicles. The incidence of bilateral seminiferous tubular atrophy in the testes was significantly increased at 650 ppm in male rats (68% vs 20% for controls, $p<0.01$). In contrast, significantly fewer 650 ppm male rats (12%, $p<0.01$) had unilateral seminiferous tubular atrophy compared with controls (38%). The incidence of bilateral seminiferous tubular atrophy was not significantly increased in the 100 and 300 ppm group, but the average severity of the lesion was greater in all treated groups than in the controls. The incidence of unilateral + bilateral seminiferous tubular atrophy also was significantly increased in 650 ppm male rats compared with that of controls. Seminiferous tubular degeneration was observed in one 100 ppm, three 300 ppm, and four 650 ppm male rats compared with none of the controls; the incidence was not significantly increased but showed a positive dose-related trend. Male rats at 650 ppm also had significantly increased ($p<0.01$ or <0.05) incidences of epididymal lesions: no spermatozoa or reduced number of spermatozoa, abnormal spermatogenic cells in the duct, epithelial vacuolation in the duct, and intraepithelial lumina. The incidences of these lesions in the 650 ppm group ranged from 31% to 49% except for abnormal spermatogenic cells, which was 78%; the control incidences were 14-17% and 34% for abnormal spermatogenic cells in the duct. The incidence of no epididymal spermatozoa in the 300 ppm group in males was 32% ($p<0.01$) compared with 15% for the control group. The total incidence of no epididymal spermatozoa and reduced number of epididymal spermatozoa combined in the 300 and 650 ppm group in male rats was 47% ($p<0.05$) and 80% ($p<0.01$),

respectively, compared with 29% for the controls. The average severity of abnormal spermatogenic cells in the duct showed a clear dose-related trend. Although the average severity of reduced number of epididymal spermatozoa was increased at 650 ppm, a clear trend was not observed for this finding. At 650 ppm, male rats also had increased incidences of acinar atrophy (N.S.), reduced colloid ($p<0.05$) in the prostate, and seminal vesicle atrophy (N.S.). Increased incidences of reduced colloid in the prostate was also observed at 300 ppm ($p<0.01$).

Female rats in the carcinogenicity phase had increased incidences of brain depression due to enlarged pituitary glands, and absent corpora lutea in the ovaries at all doses compared with control incidences. The incidence of the ovarian finding was within the range of historical controls and the brain depression was due to pituitary tumors that were found in a large number of females in all groups.

Table 3. Non-Neoplastic Histopathological Findings in Rats Treated With Ethaboxam in the Diet for up to 104 Weeks. [a]

Organ/Lesion	Dietary concentration (ppm)			
	0	100	300	650
Males – Toxicity study – 52 weeks				
Epididymides [No. examined]	[19]	[20]	[20]	[18]
No spermatozoa	0	0	1	0
Reduced no. spermatozoa	1	2	1	3
Abnormal spermatogenic cells in duct	0	3 (1.67)b	4 (2.00)	7** (1.86)
Epithelial vacuolation in duct	4	7	6	7
Intraepithelial lumina	0	0	1	2
Testes [No. examined]	[19]	[20]	[20]	[18]
Seminiferous tubular atrophy, unilateral	0	1 (2.00)	2 (2.50)	1 (4.00)
Seminiferous tubular atrophy, bilateral	1 (2.00)	3 (1.67)	4 (1.75)	5 (1.80)
Total	1	4	6†	6 ‡
Males – Carcinogenicity study				
Epididymides [No. examined]	[59]	[59]	[60]	[59]
No spermatozoa	9	8	19‡	29**
Reduced no. spermatozoa	8 (2.25)	4 (2.25)	9 (1.78)	18* (2.72)
Abnormal spermatogenic cells in duct	20 (1.70)	12 (1.83)	29 (2.10)	46** (2.24)
Epithelial vacuolation in duct	10	11	16	23*
Intraepithelial lumina	8	7	13	27**
Testes	[60]	[60]	[60]	[60]
Seminiferous tubular atrophy, unilateral	23	15	15	7 ‡‡
Seminiferous tubular, atrophy, bilateral	12 (2.17)	6 (3.50)	17 (3.18)	41** (3.61)
Seminiferous tubular atrophy, total	35	21	32	48‡‡
Seminiferous tubular degeneration	0	1	3	4
Prostate	[60]	[59]	[60]	[60]
Acinar atrophy	1	2	1	4
Reduced colloid	1	4	10‡‡	7‡
Seminal vesicle [No. examined]	[60]	[60]	[60]	[59]
Atrophy	6	7	1	12

Females – Toxicity study – 52 weeks				
Pancreas [No. examined]	[20]	[0]	[0]	[20]
Focal acinar cell atrophy	0	0	0	7**
Pituitary [No. examined]	[20]	[5]	[4]	[20]
Hyperplasia, pars distalis	0	0	0	6*
Ovaries [No. examined]	[20]	[5]	[4]	[20]
Absent corpora lutea	2	2	2	8‡
Females – Carcinogenicity study				
Brain	[60]	[52]	[51]	[60]
Depression due to enlarged pituitary	26	34*	40**	43**
Ovaries	[60]	[50]	[49]	[60]
Absent corpora lutea	17	24*	26*	33**
Historical control incidence	Range = 40-64%; average = 57%			

Data taken from pages 37-41 (toxicity study for males) and Table 12 (pp. 176-186, 191-206, 218-240), MRID 46387811.

[a]Animals in the toxicity study that died before week 52 are excluded because data on severity of the lesions in animals dying early were not included in the text tables (pp 37-38), MRID 46387811.

[b]Average severity of affected animals: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked

*p≤0.05, **p≤0.01; statistically significant, treated group compared with the control, reported by the study author

†p≤0.06; ‡p≤0.05, ‡‡p≤0.01, statistically, treated group compared with the control, calculated by the reviewer.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC concluded that the highest dose tested (650 ppm) in male and female rats was adequate, but not excessive, to assess the carcinogenicity of ethaboxam.

There were no significant treatment-related effects on mortality. At the doses tested, the number of surviving male and female rats in all groups met the minimal requirements of 50% at week 78 and 25% at week 104.

Body weight gain was significantly ($p<0.01$) decreased by 11% and 20% in males at 300 and 650 ppm, respectively, and by 10%, 10%, and 17% at 100, 300, and 650 ppm in females, respectively, during week 1 of the study. After week 1, the 100 and 650 ppm males lost more weight than controls during weeks 74-104. At 650 ppm, females weighed up to 12% less than controls throughout the remaining weeks of the study and gained 10% ($p<0.01$) less weight than controls during the first year and 16% ($p<0.05$) less over the entire study.

Other indications of exposure to ethaboxam were organ weight decreases (epididymides, seminal vesicles) at 300 and 650 ppm in males, and increased incidences of small, blue, or flaccid testes and flaccid epididymides (650 ppm males). The gross lesions corresponded with microscopic lesions seen in the testes and epididymides. These included: seminiferous tubule atrophy in the testes and epididymides, degeneration of seminiferous tubules in the testes, and absent/reduced or abnormal spermatozoa in the epididymides. Other epididymal lesions found were epithelial vacuolation in the epididymal duct and intraepithelial lumina. Microscopic lesions were also observed in the seminal vesicle (atrophy and acinar atrophy) and the prostate (reduced colloid).

2. *Carcinogenicity Study in CD-1 Mice*

Carcinogenicity Study by Dietary Administration to CD-1® Mice 78 Weeks (2002). Laboratory Project No. LKF 012. July 10, 2002. **MRID 46387810**

A. Experimental Design

Ethaboxam (99.0% a.i.) was administered in the diet to Crl:CD-1(ICR)BR mice (50/sex/dose) at dose levels of 0, 100, 300, or 900 ppm (approximately equivalent to 0, 12, 35, or 117 mg/kg/day in males and 0, 14, 44, or 135 mg/kg/day in females) for up to 78 weeks.

B. Discussion of Survival and Tumor Data

Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of ethaboxam in male mice (Memo, L. Brunsman, 1/25/06, TXR# 0054055). Survival of 900 ppm males and females at study termination (78% and 56%, respectively) was not significantly lower than their respective control groups (70% and 68%, respectively). The lowest survival in females at study termination was in the 300 and 900 ppm groups (56%). In males, the lowest survival was seen in the control group and at 300 ppm (70%). Survival in both sexes met the guideline requirements of 50% at Week 65 and 25% at Week 78.

Tumor Analyses

Males
Male mice had a statistically significant trend for liver adenomas and/or carcinomas combined at $p<0.05$ (Table 4). There were no statistically significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the male mice were based upon the Exact test for trend and Fisher's Exact test for pair-wise comparisons (Memo, L. Brunsman, 1/25/06, TXR# 0054055).

The historical control data for hepatocellular tumors in male mice, provided by the Registrant, included data from 7 studies (50-56 animals/study). The study dates ranged from March 1994-August 1997. The historical control range for hepatocellular adenomas was 7/50-12/50 and for hepatocellular adenocarcinomas was 1/50-6/50.

Historical control data from Charles River Laboratories (Giknis and Clifford, 2000), included data for 2571 livers from male CRl:CD-1(ICR) BR control mice tested approximately 78-104 weeks in 46 studies initiated between 1987-1996. Of these livers, 269 (10.5%), in 44 separate studies, had adenomas. In the 44 studies where tumors were observed, the percent affected

ranged from 2.9-28%. Carcinomas were present in 136 livers (5.3%) in 39 studies. In the 39 studies with tumors, the percent affected ranged from 1.5-16%.

Females

There were no treatment-related tumors observed in female mice.

Table 4. Ethaboxam - Crl:CD-1(ICR)BR Mouse Study (MRID 46387810)

Male Liver Tumor Rates[+] and Fisher's Exact Test and Exact Test for Trend Results

	Dose (ppm)			
Tumor Type	0	100	300	900
Adenomas (%)	13/45 (29)	12[a]/48 (25)	17/47 (36)	19/46 (41)
p =	0.05580	0.74429	0.30109	0.15374
Carcinomas (%)	0/45 (0)	4/48 (8)	2/47 (4)	2[b]/46 (4)
p =	0.4150	0.06664	0.25824	0.25275
Combined (%)	13/45 (29)	13[c]/48 (27)	18[d]/47 (38)	20[d]/46 (43)
p =	0.04305*	0.66469	0.23177	0.10934

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

[a]First adenoma observed at week 59, dose 100 ppm.
[b]First carcinoma observed at week 59, dose 900 ppm.
[c]Three animals in the 100 ppm dose group had both an adenoma and a carcinoma.
[d]One animal in each of the 300 and 900 ppm dose groups had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical controls: range, hepatocellular adenoma = 7/50-12/50, hepatocellular adenocarcinoma = 1/50-6/50

C. Non-Neoplastic Lesions in CD-1 Mice

The non-neoplastic lesions observed in male and female mice treated with ethaboxam are presented in Table 5. The incidences of liver centrilobular hepatocyte hypertrophy and eosinophilic foci were slightly increased in males (18/50 and 9/50, respectively) and females (4/50 and 2/50, respectively) at 900 ppm, compared to controls (males,11/50 and 5/50; females, 0/50 and 0/50, respectively). Borderline statistically significant ($p<0.05$) increased incidences of lung alveolar macrophage aggregations (7/50) and perivascular lymphoid cells (6/50) were seen in males at 900 ppm compared to the controls (1/50 and 1/50, respectively). Increased incidences (9/50 vs 0/50 controls) of focal interstitial cell hyperplasia in the testes were seen at 300 ppm, but the increase was not dose-related. No statistically significant microscopic findings were seen in females.

Table 5: Non-Neoplastic Lesions in Mice after up to 78 weeks of treatment with Ethaboxam in the diet[a]

Type of Lesion	0 ppm	100 ppm	300 ppm	900 ppm
Males (n=50)				
Liver, centrilobular hepatocyte hypertrophy	11	15	12	18
Liver, eosinophilic foci	5	3	4	9
Lung, alveolar macrophage aggregations	1	0	0	7+
Lung, perivascular lymphoid cells	1	3	4	6
Testes, focal interstitial cell hyperplasia	1	6	9**	5
Females (n=50)				
Liver, centrilobular hepatocyte hypertrophy	0	2	3	4
Liver, eosinophilic foci	0	0	2	2
Lung, alveolar macrophage aggregations	6	3	2	6
Lung, perivascular lymphoid cells	3	6	3	5

[a] Data obtained from pages 94-128, MRID 46387810.
* Significantly different ($p<0.05$) from the control by the study authors.
+ Significantly different ($p<0.05$) from the control, Fisher's exact test by the reviewer.
++ Significantly different ($p<0.01$) from the control, Fisher's exact test by the reviewer.

D. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC considered the highest dose tested (900 ppm) in male and female mice to be adequate, but not excessive, to assess the carcinogenicity of ethaboxam.

There were no significant treatment-related effects on mortality. At the doses tested, the number of surviving males and females in all groups met the minimal survival requirements of 50% at Week 65 and 25% at Week 78.

Body weight (9%) and body weight gain (20%) were decreased in males and females at 900 ppm compared with the control groups. The overall food efficiency during the 78-week study was also decreased in males (16%) and females (19%) at 900 ppm. Food consumption values for treated animals in both sexes were comparable to controls.

Increases in relative (to body weight) liver weight (20%) in females, increased incidences of centrilobular hepatocyte hypertrophy (36% vs 22% controls) and liver eosinophilic foci (18% vs 10% controls) were also observed at 900 ppm. In addition, there were increases in the incidences of lung alveolar macrophage aggregations (14%) and presence of perivascular lymphoid cells (12%) in males compared to the control group (2%). Testicular focal interstitial cell hyperplasia incidence was significantly increased in males at 300 ppm (18%) and 900 ppm (10%) compared to the controls (2%), but the increases were not dose related.

IV. TOXICOLOGY

1. Metabolism

In a five-day metabolism study (MRID 46378533), either [^{14}C-thiazole]LGC-30473 or [^{14}C-thiophene]LGC-30473 was administered by oral gavage or cannula (for bile-duct cannulated rats) to groups of Sprague-Dawley rats at doses of 10 or 150 mg/kg. To assess excretion, tissue distribution, and metabolism, groups of 4 rats were administered a single oral dose of 10 or 150 mg/kg of the thiazole or thiophene radiolabeled compound, or 10 mg/kg of the thiazole radiolabeled compound orally once daily for 14 days. Biliary excretion was assessed in groups of 4 bile-duct cannulated rats/sex administered a single dose of 10 or 150 mg/kg of the thiazole labeled compound. Plasma and blood cell pharmacokinetics were assessed in groups of 12 rats/sex administered a single oral dose 10 or 150 mg/kg of the thiazole or thiophene radiolabeled compound, or 10 mg/kg of the thiazole radiolabeled compound orally once daily for 14 days.

Mass balance was acceptable for the studies, ranging from 88-94% for the biliary excretion study and 96-105% for the excretion, tissue distribution, and metabolism studies. Most of the radiolabeled compound was excreted in the feces or urine within 48 hours of administration, regardless of radiolabel, dose, or sex. For both radiolabels, fecal and urinary excretion combined accounted for 96-104% of the administered dose. The main route of excretion was feces, accounting for 66-74% of the single or repeated administered low-dose, followed by urine accounting for 23-30% of the administered low-dose. Increasing the dose to 150 mg/kg resulted in more compound being excreted in the feces and less in the urine: fecal excretion accounted for 83-92% of the administered dose, while urine accounted for 13-17% of the administered dose. Results were similar in the biliary excretion study, where the percentage of thiazole radiolabeled compound absorbed in males and females within 48 hours of dosing was 71 and 72%, respectively, for the low dose, and 48 and 61%, respectively, for the high-dose.

Tissue distributions studies demonstrated that minimal amounts (<1% of the dose) of the radiolabeled compound were retained in the tissues up to 120 hours post dosing. The thyroid

generally contained the highest μg equivalents/g of the thiazole label, but only minimal amounts of the thiophene label. The liver. kidney, blood cells, and whole blood contained the next highest equivalents, with comparable equivalents measured for both radiolabels.

Pharmacokinetic studies found minimal differences between the thiazole or thiophene label. Except for the longer $t_{1/2}$ in blood cells, blood cell pharmacokinetic values were generally comparable to or lower than plasma values. The $t_{1/2}$ was similar following single administration of both the low- and high-dose, while the C_{max}, t_{cmax}, and the AUC_{120} were higher following the high-dose compared to the low-dose. However, as stated by the author, the increases were not proportional to dose and suggest capacity limited absorption of radioactivity. Compared to single dosing of the thiazole radiolabelled compound, repeated administration of the low-dose resulted in slight increases in plasma C_{max} and notable increases in $t_{1/2}$ and AUC_{120}. Female rats had higher maximum mean plasma radioactivity concentrations, higher plasma AUC_{120}, and longer terminal plasma half-life.

Minimal quantitative differences were noted within the metabolic profiles of urine, feces, or bile from rats administered the same doses of compound with the thiazole or thiophene label, following single or repeated oral administration of the low-dose of the thiazole label, or between sexes. The major urinary radioactive component was LGC-32801, followed by LGC-32800. The major fecal component was the parent compound (LGC-30473), followed by LGC-32802, LGC-32803 and LGC-32801. The main biliary radioactive components were LGC-32801 and LGC-32794.

The proposed biotransformation pathway is as follows: LGC-30473 was N-deethylated to form LGC-32794 followed by oxidation of the thiazole sulfur to LGC-32800. LGC-30473 also underwent enolisation. In one pathway, the enol form underwent hydrolysis to the amide LGC-32801, while in the other pathway, the enol underwent sulfate conjugation to LGC-32802 and hydroxylation/sulfate conjugation to LGC-32803.

The metabolism study (MRID 46378533) is classified Acceptable/Guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in the rat.

2. Mutagenicity

Ethaboxam was tested in four genetic toxicology studies. The results indicate that ethaboxam is not mutagenic in bacteria or cultured mammalian cells. It is also not clastogenic or aneugenic *in vivo* in a bone marrow mouse micronucleus assay. The Committee recommends that the *in vitro* cytogenetics assay be repeated to clarify the earlier results.

GENE MUTATIONS

- Ethaboxam was not mutagenic in independently conducted *Salmonella typhimurium* and *Escherichia coli* mammalian microsome reverse gene mutation assays (MRID 46378529) up to the limit dose (5000 μg/plate +/- S9 activation). The first trial utilized the conventional plate incorporation approach and the second trial used the pre-incubation modification to this procedure. The study is **acceptable**.

- The test material was not mutagenic in the mouse lymphoma L5178Y cell forward gene mutation assay (MRID 46378530) up to cytotoxic concentrations (300 μg/mL- S9 ;≥150 μg/mL- S9). The study is **acceptable**.

CHROMOSOME ABERRATIONS

- In the human lymphocyte cytogenetics assay (MRID 46378531), ethaboxam induced significant ($p<0.01$) increases in chromosome aberrations and a marked increase in the mitotic index (MI) at a concentration of 250 μg/mL - S9 after a 3-hour exposure and at 100 μg/ml after a 19-hour continuous exposure. The most frequently observed aberration was chromatid breaks suggesting a cytotoxic effect; this observation is supported by the severe cytotoxicity reported as necrotic cells and a reduction in scoreable metaphases at higher concentrations (≥500 μg/mL, 3-hr exposure; ≥200 μg/mL - S9, 19 hr exposure). With S9-activation, no firm conclusion can be reached because the levels showing significant increases ($p<0.01$) in chromosome aberrations (125 and 250 μg/mL + S9) were not evaluated in the repeat because of severe cytotoxicity at ≥200 μg/mL; no explanation was given for excluding 100 μg/mL + S9 from testing. Similarly, no explanation was presented for the marked increases in the MIs of cells treated with concentrations as low as 20 μg/mL -S9 (626% vs 100% for the solvent control) or 60 μg/mL +S9 (145 % vs 100% in the solvent control). In agreement with the earlier nonactivated findings, chromatid breaks was the most frequently observed structural aberration. Since no definitive conclusions can be reached, the study is **unacceptable.**

- In an *in vivo* rat micronucleus assay (MRID 46378532), the test material did not induce a clastogenic or aneugenic response in bone marrow cells harvested from male mice administered single oral gavage doses up to the limit dose (2,000 mg/kg). Overt toxicity but no cytotoxicity to the target organ was seen at the limit dose. The lack of testing females was not viewed as a study discrepancy because no sex specificity was seen in the preliminary dose range finding phase of testing. This study is **acceptable.**

3. Structure-Activity Relationship

Per correspondence with Alberto Protzel and Yin-tak Woo, the 2-amino thiazole moiety can be considered a structural alert for ethaboxam. The thiazole ring is pseudo aromatic and the addition of the amino group makes it a heterocyclic amine that could be metabolically activated to an electrophilic intermediate. There are two chemicals that have been identified as structurally similar to ethaboxam; metosulfovax and thifluzamide. Although these chemicals are similar in structure, they lack the amino thiazole moiety and it is unlikely that they would be suitable structural analogs. Therefore, there are no clear analogues for ethaboxam at this time. Toxicity information is currently unavailable for metosulfovax and thifluzamide.

4. Subchronic, Chronic, and Reproductive Toxicity

a) Subchronic Toxicity

90-Day Oral Toxicity - Rat (870.3100)

In a 13-week oral toxicity study (MRID 46387805), Ethaboxam (LGC-30473, 99.2 %, a.i.) was administered to 10 Crl:CD BR rats/sex/dose in the diet at concentrations of 0, 200, 650, or 2000 ppm (equivalent to 16.3, 49.7, and 154 mg/kg/day males, and 17.9, 58.0, and 164 mg/kg/day females).

By study termination, 7/10 high-dose female rats had developed alopecia. No alopecia was found in the control or other treatment groups. The body weight of high-dose male and female groups was significantly decreased within one week (14% and 11%, respectively) of treatment and remained decreased throughout the study (males, 14-21%; females, 11-16%, respectively). Total body weight gain of the high-dose male and female rats for the study was ~67% of their respective control groups. This was accompanied by an ~20% decrease in food consumption.

No significant treatment-related effects were found on mortality, hematology, opthalmoscopic, or urinalysis parameters. An increased relative liver weight (to body weight) of high-dose male and female rats and centrilobular hypertrophy was found in most high-dose male (10/10) and female (8/10) rats. Fine vacuolation of the adrenal *zona glomerulosa* was seen in 3/10 high-dose males and 8/10 high-dose females but was not observed in any other group

Severe testicular atrophy and interstitial cell hyperplasia were noted in most high-dose rats. No spermatozoa were found in the epididymides of high-dose rats and abnormal spermatogenic cells were found in some of the ducts. In rats treated at 650 ppm, abnormal spermatids were found in the testes of 4/10 rats, and abnormal spermatogenic cells were found in the epididymal ducts of 6/10 rats.

The LOAEL for males is 650 ppm (49.7 mg/kg/day) based on testicular/epididymal effects (abnormal spermatids in the testes, abnormal spermatogenic cells in

epididymal ducts). The LOAEL for females is 2000 ppm (164 mg/kg/day) based on centrilobular liver hypertrophy, fine vacuolation of the adrenal zonal glomerulosa and lower body weights. The NOAELS for male and females are 200 ppm (16.3 mg/kg/day) and 650 ppm (58.0 mg/kg/day), respectively.

This 13-week oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

90-Day Oral Toxicity - Mouse (870.3100)

In a 13-week oral toxicity study (MRID 46387802) Ethaboxam (LGC-30473, 99.0% a.i.) was administered to groups of 10 mice/sex at concentrations of 0, 200, 450, 1000, or 2500 ppm in the diet (equivalent to 0, 33, 74, 163, or 405 mg/kg bw/day in males and 0, 41, 93, 195, or 483 mg/kg bw/day in females).

There were no clinical signs observed in the study. One high-dose male died during week 8; otherwise, there were no effects on survival/ mortality and no additional deaths were recorded. Final body weights in males in the control through high-dose group (47, 44, 46, 42, and 44 g) and in females in the control through high-dose group (34, 36, 33, 34, and 33 g) did not show a clear dose-response effect; mean male body weights in the 1000 and 2500 ppm groups were 89 and 94% of the control group weight, respectively. The overall mean body weight gains were significantly decreased in males at 1000 ppm (9.5±2.7 g) and 2500 ppm (9.6±2.0 g) compared to the control group (13.8±5.8 g). The mean body weight gains of treated females were significantly higher than that of the control over the first 4 weeks of the study, but increases were not dose-related. The weight gain in females at 450, 1000, and 2500 ppm over treatment weeks 4-13 were slightly less than that of the control group, but the differences were not statistically significant and did not show a dose relationship. The overall weight gains in treated females were not significantly different from the control group at study termination. Treated mice tended to eat less food than the control groups, but the differences in males were not statistically significant and did not show a clear dose effect. Females at 2500 ppm ate significantly less food than the control group throughout the study. The overall food efficiency (g weight gained/g food consumed X 100) calculated by the reviewer was decreased in males at 1000 (1.63) and 2500 ppm (1.62) compared to the control group (2.25). Food efficiency in females did not show any treatment-related decrease.

Hematology parameters were not measured in the study.

The relative mean liver weights (to body weight) in males were significantly increased by 8.6% at 450 ppm ($p<0.05$), by 12.7% at 1000 ppm ($p<0.01$), and by 35.3% at 2500 ppm ($p<0.01$) compared to the control group. The relative liver weights in females were increased significantly by 12% at 1000 ppm ($p<0.05$) and by 42.1% at 2500 ppm ($p<0.01$).

The incidence of liver centrilobular hepatocyte hypertrophy was increased in males at 450 ppm (50%, p <0.05), 1000 ppm (80%, p<0.01), and 2500 ppm (90%, p<0.01) compared to the control group (0%). The centrilobular hepatocyte hypertrophy incidence in females was increased at 1000 ppm (40%, p<0.01), and at 2500 ppm (80%, p<0.01) compared to the controls (0%). The severity of the liver findings also significantly increased with increasing dose in both sexes. There were no other treatment-related microscopic findings.

The LOAELs for males and females are 450 ppm (74 mg/kg/day) and 1000 ppm (195 mg/kg/day), respectively, based on increased liver weights in association with centrilobular hepatocyte hypertrophy. The NOAELs are 200 ppm (33 mg/kg/day) in males and 450 ppm (93 mg/kg/day) in females.

This 13-week oral toxicity study in the mouse is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice.

b) Chronic Toxicity

Combined Chronic Toxicity/Carcinogenicity - Rat (870.4300)

In a combined chronic toxicity/carcinogenicity study (MRID 46387811), Ethaboxam (LGC-30473, 99.0% a.i.) was administered in the diet to groups of 60 male and 60 female Crl:CD rats at concentrations of 0, 100, 300, or 650 ppm (equivalent to 0, 5.5, 16.4, or 35.8 mg/kg bw/day in males and 0, 7, 21, or 45.5 mg/kg bw/day in females) for 104 weeks (carcinogenicity phase). Groups of 20 males and 20 females were administered the same diets and sacrificed at 52 weeks (chronic toxicity study).

No treatment-related clinical signs, effects on survival/mortality, abnormalities of the eyes (ophthalmoscopic examination), hematologic changes, or urinalysis changes were observed in any group of male or female rats receiving any dose of the test material. No treatment-related neurological effects were observed during the functional observational battery (FOB). Statistically significant clinical chemistry changes were observed in male and female rats, but were not considered adverse since there were no corresponding histopathological lesions. Body weight gain was significantly decreased by 11% and 20% in mid- and high-dose males, respectively, and by 10%, 10%, and 17% in low-, mid-, and high-dose group females, respectively, during week 1 of the study; otherwise, no treatment-related effect was observed on body weight or weight gain in males or low- or mid-dose females. High-dose group females weighed up to 14% less than controls throughout the remaining weeks of the study and gained 10% ($p \leq 0.01$) less weight than controls during the first year, 93% less during the second year, and 16% ($p \leq 0.05$) less over the entire study. Food consumption was within 8% of control level throughout the study and food efficiency was similar to that of controls over the first 14 weeks of the study.

Organ weight changes, gross lesions, and microscopic lesions observed in male rats indicated that the male reproductive organs were targets for LGC-30473. No treatment-related changes in organ weights were observed in male rats at 52 weeks, but epididymal weight was significantly decreased in mid- and high-dose males and seminal vesicle weight was significantly decreased in high-dose group males compared with the controls at 104 weeks. Gross examination showed an increased incidence of small testes in mid- and high-dose male rats at week 52 and significantly increased incidences of small, blue, or flaccid testes and small or flaccid epididymides in high-dose males in the carcinogenicity study compared with control incidences. The gross lesions corresponded with microscopic lesions observed in the testes and epididymides. The incidence of unilateral/bilateral seminiferous tubular atrophy in the testes was 6/18 ($p<0.05$) in high-dose males and (6/20, $p<0.06$) in mid-dose males compared with 1/19 controls at 52 weeks. The incidence of abnormal spermatogenic cells in the epididymal duct was 7/18 ($p<0.01$) in high-dose males and 0/19 in controls at 52 weeks. In the carcinogenicity phase of the study, bilateral seminiferous tubular atrophy in the testes was observed in 41/60 ($p<0.01$) high-dose males and 12/60 controls, but unilateral seminiferous tubular atrophy was observed in only 7/60 ($p<0.01$, negative trend) high-dose males and 23/60 controls. Degeneration of the seminiferous tubules in the testes was found in 3/60 (not statistically significant; N.S.) and 4/60 (N.S.) mid- and high-dose males, respectively, and 0/60 controls. The incidence of epididymides with no spermatozoa was 19/60 and 29/59 ($p<0.01$) in mid- and high-dose males, respectively, compared with 9/59 in controls, and the incidence of epididymides with reduced number of spermatozoa was 18/59 ($p<0.05$) in high-dose males compared with 8/59 in controls. Other epididymal lesions found at significantly increased incidences in high-dose males included abnormal spermatogenic cells and epithelial vacuolation in the epididymal duct and intraepithelial lumina. Microscopic lesions also were observed in the seminal vesicle and prostate. The incidence of seminal vesicle atrophy and acinar atrophy in the prostate was increased, but not significantly, in high-dose males and reduced colloid in the prostate was significantly increased in mid- and high group males. The non-neoplastic findings in male rats suggest that LGC-30473 is a potential endocrine disruptor affecting the male reproductive organs.

In female rats, no treatment-related lesions were observed at 52 weeks or in the carcinogenicity study. The incidences of lesions that were significantly increased at 52 weeks at the high dose (focal acinar cell atrophy and pituitary pars distalis hyperplasia) were not significantly increased in the carcinogenicity study, and the incidence of ovaries with no corpora lutea was within range of historical controls.

The LOAEL for males is 300 ppm (16.4 mg/kg bw/day) based on effects in male reproductive organs (testes, epididymides, prostate, and seminal vesicles) and the LOAEL for females is 650 ppm (45.5 mg/kg bw/day) based on decreased body weight and body weight gain. The NOAEL for males is 100 ppm (5.5 mg/kg bw/day) and the NOAEL for females is 300 ppm (21.0 mg/kg bw/day).

At the doses tested, there was some evidence of carcinogenicity in male rats based on a significantly increased incidence of interstitial (Leydig) cell adenoma in the mid and high-dose groups compared with the control group. The incidence was 1/60 (2%), 4/60 (7%), 6/60 (10%, $p<0.05$), and 7/60 (12%, $p<0.05$) at 0, 100, 300, and 650 ppm, respectively. The incidence of interstitial cell adenoma in the testes also exceeded that of historical controls, which ranged from 0-6.2% with an average of 2.5%. The test material produced non-neoplastic lesions in the testes, epididymides, seminal vesicles, and prostate and neoplastic lesions in the testes indicating that the mode of action of LGC-30473 is possibly endocrine disruption affecting the pituitary-gonadal axis in males.

The incidence of pituitary pars distalis adenoma was 32/60 (53%), 39/60 (65%), 43/60 (72%, $p<0.01$), and 36/60 (60%) and the incidence or pars distalis adenoma/adenocarcinoma combined was 42/60 (70%), 48/60 (80%), 51/60 (85%, $p<0.05$), and 51/60 (85%, $p<0.05$) in females at 0, 100, 300, and 650 ppm, respectively. The incidences of the adenoma in mid-dose group females and adenoma/adenocarcinoma combined in mid- and high-dose group females were slightly above the upper range of historical controls; nevertheless, the lack of a clear dose-related trend and the extremely high incidence in controls suggest that the increased incidences are not treatment related. The rats were adequately dosed to test for carcinogenicity as evidenced by decreased weight gain in female rats and non-neoplastic lesions in the reproductive organs in male rats.

This chronic toxicity/carcinogenicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study [OPPTS 870.4300); OECD 453] in rats.

Carcinogenicity Study - Mouse (870.4200b)

In a 78-week oral carcinogenicity study (MRID 46387810), LGC-30473 (99.0% a.i., lot # P980622) was administered to groups of 50 Crl:CD-1®(ICR)BR mice/sex/dose in the diet at 0, 100, 300, or 900 ppm (approximately 0, 12, 35, or 117 mg/kg/day in males and 0, 14, 44, or 135 mg/kg bw/day in females).

There were no treatment-related effects on mortality or clinical signs. The mean final body weight of males and females at 900 ppm was decreased by 9% compared with the control groups. The mean body weight gain of males and females at 900 ppm was decreased by 20% compared to the control groups. The food consumption was similar in all groups of males and females. The overall food efficiency during the 78-week study was decreased by about 16% in males and 19% in females at 900 ppm compared to the control group. The differential blood counts did not reveal any physiologically significant changes at 52 or 78 weeks.

The group mean liver weight adjusted for body weight was significantly increased by about 20% in females at 900 ppm compared to the control group. Incidences of centrilobular hepatocyte hypertrophy (36%) and liver eosinophilic foci (18%) were

increased in males at 900 ppm compared to the control group (22% and 10%, respectively), but the differences were not statistically significant. The incidences of lung alveolar macrophage aggregations (14%) and presence of perivascular lymphoid cells (12%) in males at 900 ppm were increased compared to the control group (2%). Testicular focal interstitial cell hyperplasia incidence was significantly increased in males at 300 ppm (18%) and 900 ppm (10%) compared to the controls (2%), but the increases were not dose related.

The LOAEL is 900 ppm (117 mg/kg/day in males and 135 mg/kg/day in females) based on decreased weight gain and food efficiency in both sexes. The NOAEL is 300 ppm (35 mg/kg/day in males and 44 mg/kg/day in females).

Treatment of Crl: CD-1®(ICR)BR mice at dietary levels of LGC-30473 up to 900 ppm for up to 78 weeks did not result in a significant increase in the incidence of individual neoplasms compared to the control groups. However, the incidence of hepatocellular adenoma in males at 900 ppm (38%, NS) was increased compared to the control group (26%), and was near the upper range seen in historic control animals (~14-40%). Combining the liver adenoma and carcinoma incidences resulted in the combined incidence (40%) being significantly different (p=0.048) from the control group (26%). The liver neoplasms were not increased in high-dose females compared to the control group.

This carcinogenicity study in mice is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

c) Reproductive Toxicity

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 46387804), LGC-30473 (99.0%, lot #P980622) was administered to thirty-two Crl:CD®BR (Sprague Dawley origin) rats/sex/dose in the diet at concentrations of 0, 65, 200, or 650 ppm. Premating doses for the F_0-generation parental animals were 0, 5.2, 16.2, or 52.6 mg/kg bw/day for males, and 0, 5.7, 17.6, or 56.1 mg/kg bw/day for females. One litter was produced in each generation. Parental animals of both generations were administered test or control diets for 10 weeks prior to mating, and throughout mating, gestation, and lactation.

The adverse effects on the two generations of parental rats and their offspring occurred only at 650 ppm. There were no treatment-related effects at 65 or 200 ppm and the results reported in this summary are for the high-dose groups and the controls, only.

Signs of parental systemic toxicity included body weight changes, reduced food consumption, organ weight changes, and microscopic changes in reproductive tissues. The F_0 males showed no significant changes in absolute body weight, but their body weight gain was decreased, in comparison to control values, by 10.5-22% ($p<0.01$)

during weeks 1-3 of premating. Body weight, weight gain, and food consumption of the treated F_0 females were comparable to control values throughout premating. The F_1 males had reduced absolute body weight, significantly different from controls during week 0 to week 6 of premating ($p<0.01$; decreases of 10.3-17.4%). Body weight gain was decreased during weeks 1-5 ($p<0.01$, reductions of 10.7-14.5%). Among the F_1 females, decreases in body weight were significantly different from controls throughout premating ($p<0.01$, decreases of 7.0-12.9%). Food consumption was decreased for the F_1 males during weeks 2-5 and for the females during weeks 4, 6, 7, and 9 ($p<0.01$; about 10-13%).

Significant weight changes were observed for the following organs: reduced absolute adrenal weight of the F_0 males and females and the F_1 females, reduction in the adrenal to body weight ratio of the F_0 females, and increased absolute thyroid and parathyroid weight in the F_0 females; however, necropsy revealed no macroscopic or microscopic correlates.

The parental systemic toxicity LOAEL for LGC-30473 in male and female rats is 650 ppm (52.6 mg/kg/day for males, 56.1 mg/kg/day for females), based on decreased premating body weight gain of the F_0-generation males and decreased premating absolute body weight of the F_1 males and females. The parental systemic toxicity NOAEL for male and female rats is 200 ppm (16.2 mg/kg/day for males, 17.6 mg/kg/day for females).

With regard to offspring viability, the only significant ($p<0.05$) finding for the F_1 pups was a viability index of 80.9% compared with 94.5% for the controls. For the more severely affected F_2 generation, significant reductions were observed in mean live litter size throughout lactation ($p<0.05$ or 0.01). The live birth index of 84.8% and viability index of 77.5% were significantly lower ($p<0.01$ for both) than the control values of 93.8% and 99.7%, respectively. Decreased body weight was observed at 650 ppm in the F_1 male and female pups from day 14 to day 21 of lactation ($p<0.01$, decreases of 13.1-15.7%) and in the F_2 male and female pups from day 14 to day 28 ($p<0.01$, decreases of 12.4-18.2%). Overall body weight gain from day 1-21 (F_1 pups) and 1-28 (F_2 pups) was also reduced. No clinical signs were observed during lactation of either generation of pups and no treatment-related systemic effects were observed in either generation at 65 or 200 ppm. Lower body weight of the F_1 pups at 650 ppm resulted in a delay in sexual maturation of 2.4 days for males and 2.1 days for females.

The offspring systemic toxicity LOAEL for LGC-30473 in male and female rats is 650 ppm (52.6 mg/kg/day for males, 56.1 mg/kg/day for females), based on decreased body weight and decreased viability of the F_1 and F_2 males and females during lactation. The offspring systemic toxicity NOAEL for male and female rats is 200 ppm (16.2 mg/kg/day for males, 17.6 mg/kg/day for females).

In addition to body weight, the male reproductive system is the apparent target for the toxicity of LGC-30473. The F_1 males exhibited reductions in the following: absolute weight of the seminal vesicle plus coagulating gland ($p<0.01$, 13.1% reduction); absolute weight of the epididymides ($p<0.01$, 16.7% reduction); relative weight of the epididymides ($p<0.05$, 11.5% reduction); and absolute weight of the testes ($p<0.01$, 14.1% reduction). Microscopic examination of the epididymides revealed a statistically significant reduction in the number of sperm and an increase in the number (percentage) of abnormal sperm. In the testes, increased incidences of tubules showing a depletion of all germ cells and of abnormal spermatids in occasional tubules were observed.

Reproductive toxicity in the F_0 parental males was also characterized by impaired sperm motility (76% motile, compared with 85% for controls; $p<0.01$) and an increased percentage of decapitate and abnormal sperm in the vas deferens (13.3%, compared with 5.0% for controls; $p<0.01$). Microscopic examination revealed abnormal spermatogenic cells in the epididymal ducts. Reproductive parameters of the F_0 females, including numbers mated and pregnant, number of live litters born, conception rate, fertility index, and gestation index, were not affected by treatment with LCG-30473.

The males of the F_1 parental generation had treatment-related reproductive effects that included reductions in the percentage of males mating (78%, compared with 100% of controls; $p<0.05$) and in the male fertility index (52%, compared with 89% of controls; $p<0.01$). Necropsy revealed increased incidences of small epididymides and testes, and microscopic examination revealed abnormal spermatogenic cells in the epididymal ducts, reduced numbers of sperm in the epididymides, depletion of germ cells and the presence of abnormal spermatids in testicular tubules.

The F_1 parental females had a reduced number of implantation sites ($p<0.05$, 19.4% reduction). No other treatment-related effects on reproduction were apparent for the F_1 parental females. The fertility index and conception rates of the F_1 females were decreased to 70 and 73%, respectively. These percentages were not statistically significant when compared to the control values of 89% for both parameters. The effects on implantation sites, fertility index and conception rate reflect the adverse, treatment-related effects on the fertility of the parental males.

The reproductive toxicity LOAEL for LGC-30473 in male rats is 650 ppm (52.6 mg/kg/day), based on testicular lesions and reduced fertility in the F_1 males. The reproductive toxicity NOAEL for male rats is 200 ppm (16.2 mg/kg/day). The reproductive toxicity NOAEL for LGC-30473 in female rats was greater than 650 ppm (greater than 56.1 mg/kg/day) and the LOAEL was not obtained.

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800; OPP §83-4; OECD 416) in rats.

5. *Mode of Action*

Mode of Action Proposal for Testicular Interstitial (Leydig) Cell Adenoma

A proposed mode of action study and position paper have been submitted (via email, 1/20/06) for ethaboxam by the Registrant. In the combined chronic/carcinogenicity study in rats, increased incidences of interstitial (Leydig) cell tumors were accompanied by non-neoplastic changes observed in the testes, epididymides, prostate, and seminal vesicles. To elucidate the mechanism leading to the tumors, a study (Laboratory Project No. LKF 066/022132) was performed investigating the effect of ethaboxam on reproductive hormones.

INVESTIGATION OF REPRODUCTIVE HORMONE LEVELS AND GENITAL TRACT PATHOLOGY IN MALE RATS AFTER EXPOSURE TO ETHABOXAM

Two groups of 10 male rats (crl:CD (SD) IGS BR) received ethaboxam, via the diet, at concentrations of 650 ppm or 2000 ppm (approximately equivalent to 34.8 and 114.3 mg/kg/day, respectively) for 13 weeks. The animals were observed for clinical signs prior to and throughout the treatment period. A detailed physical examination, bodyweight, and food consumption measurements were performed at weekly intervals. Blood samples for analysis of luteinizing hormone (LH), testosterone, and follicle stimulating hormone (FSH) were obtained before treatment, and on days 7, 14, 28, and 91 of treatment. On completion of the treatment period, all animals were sacrificed and subjected to a full necropsy; reproductive tissues were weighed and subsequently processed for histopathological examination. Hormone levels were examined by radioimmunoassay, using Diagnostic Product Corporation Coat-A-Count kit (testosterone) and Amersham Biotrak rat-specific assay kit (LH and FSH).

Dietary administration (13 weeks) of ethaboxam to CD rats at 650 and 2000 ppm was associated with evidence of general toxicity (decreased body weight/body weight gain). There were slight decreases in epididymal weights in the 650 ppm group and decreases in epididymal and testicular weights in the 2000 ppm group. At 2000 ppm, histopathological changes (Table 7) were observed that included: inflammation, cellular debris in the ducts, epithelial vacuolation, ductular multinucleated giant cells, and a reduced number of spermatozoa in the epididymides. In the testes, germ cell depletion/degeneration and bilateral interstitial cell hyperplasia were observed. Plasma testosterone concentrations were reduced (56-69%) up to day 28 in the 2000 ppm group. There was a reduction (5-17%, NS) in FSH hormone concentrations up to day 14 in males receiving 650 or 2000 ppm. High FSH (59%) and slight increases (19%) in LH levels were observed in males receiving 2000 ppm (Table 6) at day 91.

It was concluded by the Registrant that results of the study suggest that chronic stimulation of interstitial cells by elevated luteinizing hormone levels can occur following exposure to ethaboxam, with the initial effect being a reduction in testosterone.

Discussion

In the study noted above, there were significant decreases in plasma testosterone observed on days 7, 14, and 28 (statistically significant at days 7 and 14; $p < 0.05$ and $p < 0.01$, respectively) in the 2000 ppm group and on day 91 in the 650 ppm group. Although these results are somewhat confounded due to the decrease in testosterone also observed in the control group, it is supportive of pathological changes seen in the male reproductive organs in this study and other studies involving the rat. In other rat studies (combined chronic toxicity/carcinogenicity, 13 week toxicity), there were changes observed in the epididimydes (absent/reduced or abnormal spermatozoa), testes (seminiferous tubule atrophy and degeneration), prostate (acinar atrophy), and seminal vesicles (atrophy) after exposure to ethaboxam. The effects seen in these organs, all of which are androgen dependent, are bio-indicators of a decrease in testosterone. Furthermore, the 59% increase in FSH levels observed in the 2000 ppm group (day 91) is also reflective of testicular damage. A slight rise in LH (19%) was seen in the 2000 ppm group at day 91 and was considered, by the registrant, an effect of the decrease in testosterone. Although the changes in LH levels were statistically significant ($p< 0.01$), the increase of 19% over controls is considered small. Per Ralph Cooper (Chief, Endocrinology branch, RTD, NHEERL, US EPA), a more robust response of 1.5-2 fold increase compared to controls is considered indicative of elevated LH levels. Therefore, the increase in LH levels at 2000ppm is not considered toxicologically significant and the results are equivocal.

In summary, the overall weight of evidence suggests that ethaboxam is a testicular toxicant in the rat, capable of producing marked damage. However, based on this study and the available data, it is unclear whether the mechanism leading to Leydig cell tumors is a result of a hormonally-mediated pathway.

Table 6. Ethaboxam-LGC-30473-Investigation of Reproduction Hormone Levels

Blood chemistry (n=10)					
	Before treatment	D7	D14	D28	D91
Testosterone nmol/L					
0 ppm	8.4 ± 6.05	6.2 ± 3.73	4.4 ± 2.52	6.2 ± 5.35	1.9 ± 1.61
650 ppm	7.7 ± 6.97	5.9 ± 5.43 (↓5%)	4.8 ± 3.85	7.1 ± 4.93	1.0 ± 0.51 (↓47%)
2000 ppm	10.3 ± 9.71	1.9± 2.81* (↓69%)	1.4 ± 1.08** (↓68%)	2.7 ± 1.6 (↓56%)	2.2 ± 1.02
LH ng/ml					
0 ppm	1.8 ± 0.39	1.8 ± 0.29	2.3 ± 0.32	2.4 ± 0.53	2.1 ± 0.20
650 ppm	2.1± 0.47	2.0 ± 0.49	2.4 ± 0.32	2.3 ± 0.43	2.2 ± 0.27
2000 ppm	1.8 ± 0.25	1.8 ± 0.43	2.1 ± 0.24	2.2 ± 0.35	2.5 ± 0.29** (↑19%)
FSH ng/ml					
0 ppm	11.1 ± 2.46	11.2 ± 2.44	8.5 ± 2.45	9.2 ± 2.56	7.2 ± 2.24
650 ppm	12.0 ± 1.68	10.6 ± 1.48	7.3 ± 1.66	8.3 ± 1.44	6.2 ± 1.19
2000 ppm	12.9 ± 2.85	9.9 ± 2.52	7.1 ± 2.04	9.1 ± 4.00	11.5 ± 2.05** (↑59%)

*p<0.05), ** p<0.01 (Two tailed Fisher's exact probability test), statistically significant, treated group compared with the control, reported by the study author.

Table 7. Non-Neoplastic Lesions in Crl:CD BR (SD) Rats After Exposure to Ethaboxam for 13 weeks (Hormone Study)

Organ/Lesion	Dietary concentration (ppm)		
	0	650	2000
Epididymides			
Inflammation	2	2	10***
Spermatozoa absent	0	0	1
Epithelial vacuolation	0	0	4
Cellular debris in duct	0	2	10***
Reduced numbers of spermatozoa	0	0	9***
Ductular multinucleated giant cells	0	0	1
Testes			
Bilateral germ cell depletion/degeneration	0	2	10***
Bilateral presence of multinucleated giant cells	0	0	2
Bilateral interstitial cell hyperplasia	0	0	10***
Number of animals examined	10	10	10

***$p \leq 0.001$ (Two tailed Fisher's exact probability test), statistically significant, treated group compared with the control, reported by the study author.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

Rat

• In male Sprague Dawley rats, the incidence of benign testicular Leydig cell tumors was 1/56 (2%), 4/56 (7%), 6/59 (10%), and 7/58 (12%) for the control, 100, 300 and 650 ppm dose groups, respectively. The CARC considered the increase in benign Leydig cell tumors of the testes to be treatment-related based on the following:

-There was a significant increasing trend, and a significant difference in pair-wise comparison of the 650 ppm dose group with the control for benign interstitial (Leydig) cell tumors of the testes, both at $p < 0.05$.

-The incidences of interstitial cell tumors in all treated groups (7-12%) exceeded the historical control incidence rates for the testing laboratory (2.5% average, 0-6.2%, range). Therefore, the increased incidences of interstitial cell tumors at 300 ppm and possibly 100 ppm, while not statistically significant, were considered to be biologically significant.

• There were no treatment-related tumors seen in female Sprague Dawley rats.

• Adequacy of Dosing: The CARC considered the highest dose tested (650 ppm) in male and female rats to be adequate, but not excessive, to assess the carcinogenicity of ethaboxam. This was based on decreased body weight gain in males (20%) and females (17%) and toxicity of male reproductive organs, including non-neoplastic lesions of the testes, epididymides, prostate, and seminal vesicles.

Mouse

• In male CD-1 mice, the incidence of liver tumors (adenomas and/or carcinomas combined) was 13/45 (29%), 13/48 (27%), 18/47 (38%), 20/46 (43%) for the controls, 100, 300, and 900 ppm dose groups, respectively. The CARC did not consider these tumors to be treatment-related based on the following:

- Male mice had a statistically significant trend for liver adenomas and/or carcinomas combined only at $p<0.05$ ($p=0.043$). There were no statistically significant pair-wise comparisons of the dosed groups with the controls for adenomas, carcinomas, or combined adenomas and/or carcinomas.
- It is noted that the incidence of adenomas in the concurrent control (29%) was high and outside the historical control range of the testing laboratory (14-24%) as well as the historical control range from Charles River Laboratories (2.9-28%). While the incidence of liver adenomas was outside the historical control range for all treated groups, there was no significant trend or significant pairwise comparisons of the dosed groups with the controls for liver adenomas at any dose level.

- There were no treatment-related tumors seen in female CD-1 mice.

- Adequacy of Dosing: The CARC considered the highest dose tested (900 ppm) in male and female mice to be adequate, but not excessive, to assess the carcinogenicity of ethaboxam. This was based on decreased body weight body weight (9%) and body weight gain (20%) in males and females at 900 ppm, decreased food efficiency, increased liver weights in females, and liver pathology in females and lung pathology in males.

2. Mutagenicity

Based on the findings, it was concluded that ethaboxam is not mutagenic in bacteria or mammalian cells. There is, however, equivocal evidence of a clastogenic effect in the *in vitro* human lymphocyte chromosome aberration assay. In contrast, the test material was neither clastogenic nor aneugenic in the mouse bone marrow micronucleus assay up to the limit dose. Although the weight-of-evidence does not support a mutagenic concern, the Committee recommends that the *in vitro* cytogenetics assay be repeated to clarify the earlier results.

3. Structure-Activity Relationship

There are no suitable structural analogues for ethaboxam at this time, however, the 2-amino thiazole moiety can be considered a structural alert for ethaboxam.

4. Mode of Action

The overall weight of evidence suggests that ethaboxam is a testicular toxicant in the rat, capable of producing marked damage. However, based on the available data, it is unclear whether the mechanism leading to Leydig cell tumors is a result of a hormonally-mediated pathway. The existing mode of action data are inadequate as a basis for delineation of a plausible sequence of key events leading to Leydig cell tumors (i.e., decreased testosterone and chronic stimulation of interstitial cells by elevated luteinizing hormone (LH) levels). While there was a suggestion of decreased testosterone and a slight increase in LH, the hormonal data did not support a consistent pattern, either temporally or through dose-response concordance. Therefore, the decrease in testosterone and increase in LH cannot be clearly linked with increases in Leydig cell tumors.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's Final Guideline for Carcinogen Risk Assessment (March 2005), the CARC classified Ethaboxam as **"Suggestive Evidence of Carcinogenic Potential"**. This was based on the following weight-of-evidence considerations:

(i) There was a treatment-related increase in only one tumor type (benign Leydig cell tumors of the testes) in one species (Sprague Dawley rat);
(ii) No treatment-related tumors were seen in female rats or male or female mice;
(iii) Ethaboxam does not appear to be a gene mutagen, however, the clastogenic potential of this compound can not be unequivocally determined at this time;
(iv) The registrant's proposed hormonally-mediated pathway is biologically plausible, but the available data are insufficient to delineate the sequence of key events leading to Leydig cell tumors that are necessary to characterize human relevance of this animal response.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The quantification of carcinogenic potential is not required.

VIII. BIBILIOGRAPHY

MRID No.	CITATION
46387811	Paffett, R. (2002) Combined Carcinogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 Weeks: LGC-30473. Project Number: LKF/002, LKF/002/984932. Unpublished study prepared by Huntingdon Life Sciences Ltd. 2813 p.
46387810	Chambers, P. (2002) Carcinogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks: LGC30473. Project Number: LKF/012/012194, LKF/012. Unpublished study prepared by Huntingdon Life Sciences Ltd. 1315 p.
46387805	Gardner, T. (1997) Toxicity to Rats by Dietary Administration for 13 Weeks: LGC-30473. Project Number: LKY/26/963670, LKY/26. Unpublished study prepared by Huntingdon Life Sciences Ltd. 236 p.
46387802	Chambers, P. (2002) Preliminary Toxicity Study by Dietary Administration to CD-1 Mice for 13 Weeks. Project Number: LKF/011/993345, LFK/011. Unpublished study prepared by Huntingdon Life Sciences Ltd. 197 p.

46378533 Langford-Pollard, A. (2003) LGC-30473: Metabolism in Rats. Project Number: LKF/019/022799, LFK/019. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 405 p.

46378532 Mehmood, Z. (2001) LGC-30473: Rat Micronucleus Test. Project Number: LKF/046/012763, 23432O. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 45 p.

46378531 Allais, L. (2001) LGC-30473: *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes. Project Number: LFK/039/013151, GTOX/CYT/OECDHL/7, 23432M. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 44 p.

46378530 Clare, M. (2001) LGC-30473: Mammalian Cell Mutation Assay. Project Number: LFK/038, LFK/038/013376, GTOX/MCM/OECDMLAM/5. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 49 p.

46378529 May, K. (2004) LGC-30473: Bacterial Mutation Assay. Project Number: LKF/037, GTOX/BMA/OECDSTD/6. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 41 p.

---------- L.Brunsman. 2006. Ethaboxam: Qualitative Risk assessment Based on Crl:CD-1(ICR)BR Mouse and Crl:CD Rat Carcinogenicity Dietary Studies. January 25, 2006. TXR No. 0054055

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